ID 03.2

The human HepaRG cell line: a brief history of its use in genetic toxicology: advantages, limits and future directions

Ludovic LE HEGARAT

Anses- *French Agency for Food, Environmental and Occupational Health & Safety-Fougeres Laboratory-Toxicology of Contaminants Unit, 35306 Fougères CEDEX, France*

The genotoxicity assessment of chemicals is becoming increasingly dependent upon the use of in vitro models. Therefore, to take into account the impact of human metabolism in the genotoxicity response of chemicals, human liver cell lines have been studied and used in genotoxicity testing strategies. In addition to being a physiologically relevant model, HepaRG cells have been found to be an excellent model of human hepatic metabolism and toxicity, having nuclear receptor functionality, and expression of phase I and II enzymes, drug transporters, similar to primary human hepatocytes. Based on these characteristics, many researchers have focused their efforts to determine the capacity of the HepaRG cell model to detect human genotoxicants by comet assays and micronucleus tests. Their work found that this model is very sensitive and specific in genetic toxicology, and could be suitable to integrate into the current in vitro testing strategy. In addition, other biomarkers of genotoxicity have been investigated in HepaRG cells, such as γ-H2AX, expression of targeted genes (TGX-DDI, GENOMARKS), cometchip and high throughput multiparametric assays. Recently, with the development of new approach methologies (NAMs), 3D HepaRG models have been tested with the Cometchip technology and high throughput micronucleus assays, and have given promising results. Altogether these data suggest that HepaRG cells could provide a major contribution to in vitro genotoxicity assessment in in vitro genotoxicity assessement. Moreover, in the case of next-generation risk assessment of chemicals, the combination of more predictive approaches such as 3D co-culture models using HepaRG cells combined with OMICS, POD, and IVIVE approaches need to be explored.